Remarks

I. Status of the Claims

Claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31 and 32 are pending in the application, with claim 1 being the sole independent claim.

II. Summary of the Office Action

In the Office Action dated May 23, 2001, the Examiner has maintained one rejection of the claims. Applicants respectfully offer the following remarks to overcome this rejection.

III. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at page 3, lines 10-12, the Examiner has maintained the rejection of claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31 and 32 under 35 U.S.C. § 103(a) as being unpatentable over Burmer, U.S. Patent No. 5,726,022 (Doc. Ref. AH1, of record; hereinafter "Burmer") in view of Carninci *et al.*, *Genomics 37*:327-336 (1996) (Doc. Ref. AR1, of record; hereinafter "Carninci"). Applicants respectfully traverse this rejection, and reiterate and incorporate by reference herein the remarks in traversal of this rejection that were included in Applicants' Amendment and Reply Under 37 C.F.R. § 1.111 filed on March 12, 2001 and in Applicants' Preliminary Remarks filed on August 28, 2000.

The invention as presently claimed is drawn to methods of producing nucleic acid molecules using primer-adapters that comprise one or more ligands and one or more cleavage sites. Adapters are added to nucleic acid molecules in the presently claimed

methods by providing the adapters on *primer* molecules, which serve as the starting point for the synthesis of new nucleic acid molecules comprising such adapters -- the adapters are *not* ligated directly to digested nucleic acid molecules in the present methods.

As the Examiner has acknowledged in the previous Office Action (PTO Prosecution File Wrapper Paper No.18), Burmer does not disclose using a primer with one or more restriction enzyme cleavage sites (Paper No. 18, page 3, lines 14-15). Moreover, Applicants wish to remind the Examiner that, as was discussed with the Examiner in detail during the interview held on August 22, 2000, the adaptors of Burmer are *not* contained on primers used for synthesis of a nucleic acid molecule. Instead, Burmer describes *ligating* double-stranded adaptors to nucleic acid fragments.

The method disclosed by Burmer requires addition of adapter molecules to nucleic acid by first digesting nucleic acid molecules with restriction enzymes, such that the adapter-containing fragments can be ligated to them. According to the Examiner,

> Burmer does disclose that the method involves using an adapter which includes a restriction site and a ligand binding end ligated to the nucleic acid fragment of a first and second nucleic acid samples to provide the nucleic acid complementary to a primer for amplification (see column 4, lines 16-25). This suggests that the primer comprises the nucleic acid sequence which is complementary to the adaptor which includes a restriction site and a ligand binding end.

Office Action, page 2, lines 9-14. As the Examiner has stated, the primer disclosed by Burmer "comprises the nucleic acid sequence which is complementary to the adapter." According to the Examiner, the method disclosed by Burmer requires at least two steps: 1) ligation of adapter molecules to the nucleic acid fragments; and 2) use of primers with sequence complementary to the adapters. Thus, the adapters and the primers are two distinct entities.

This approach is considerably different from the presently claimed methods, wherein the adapters become a part of the product molecule by serving as primers from which the product molecule is extended by the action of the one or more polypeptides having polymerase activity and/or reverse transcriptase activity. Hence, one key to the claimed methods is that the adapter molecule, which has one or more cleavage sites and one or more ligands, also serves as the primer molecule for synthesis of the first nucleic acid molecule.

It appears the Examiner is equating the multi-step process disclosed by Burmer (digestion of nucleic acid molecules, ligation of adapters, and use of primers with sequence complementary to that of the adapters) to the claimed invention, which uses adapter molecules with one or more cleavage sites and one or more ligands as primers for the synthesis of nucleic acid molecules. Even if the claimed primer-adapters were an amalgamation of disclosed process steps, which Applicants contend is not the case, this in and of itself, does not warrant a rejection under 35 U.S.C. § 103. "Where, as here, nothing of record plainly indicates that it would have been obvious to combine previously separate process steps into one process, it is legal error to conclude that a claim to that process is invalid under § 103." *Fromson v. Advance Offset Plate, Inc.* 225 USPQ 26, 32 (Fed. Cir. 1985). Burmer therefore is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness of the presently claimed invention.

The deficiencies of Burmer are not cured by the disclosure of Carninci. In characterizing this reference, the Examiner contends that:

> Carninci et al. disclose that the method involves using a primer inserted with restriction sites, the restriction sites are incorporated into cDNA by PCR with ExTaq DNA polymerase and the amplified nucleic acid is cleaved by the restriction enzyme (see pg. 329, column 1-2, the fourth and fifth paragraph).

Office Action, page 3, lines 3-6. Based on this characterization, the Examiner concludes that one of ordinary skill in the art would have been motivated to combine the teachings of Burmer and Carninci *et al.* to make the claimed invention. *See* Office Action at page 3, lines 6-8. Applicants respectfully disagree.

Carninci fails to suggest or disclose the use of primers containing both cleavage sites and ligands. In fact, the only disclosure of the use of ligands in Carninci is for the labeling of cap structures on eukaryotic mRNA, which simply permits the capture of mRNA molecules to facilitate subsequent production of full-length cDNA. *See* Carninci in the Abstract; at page 328, column 2 through page 329, column 1; and in Figure 1 at page 330. Carninci would have provided no motivation to incorporate ligands into primer molecules. There is no disclosure in Carninci that would have led one of ordinary skill in the art to use a primer-adapter molecule containing both a ligand and a cleavage site for synthesis of a first nucleic acid molecule comprising the primer adapter (and thus comprising the ligand and cleavage site). Thus, Carninci provides no disclosure or suggestion that would cure the above-noted deficiencies of Burmer.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to

combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Absent such suggestion, motivation, and reasonable expectation of success, the cited references may not be properly combined to render the claimed invention obvious. *See Fine* at 1598. As discussed above, Burmer and Carninci, alone or in combination, do not disclose or suggest the presently claimed invention. Equally importantly, neither of the cited references contains any suggestion that its disclosure should be modified with any portion of the disclosure of the other reference in order to enable one of ordinary skill to have a reasonable expectation of success in making and using the claimed invention, without which the disclosures of these references may not be properly combined under *Fine* and *Dow*.

Moreover, the Carninci reference was already available in the art (having been published in November 1996) as of the filing date of the Burmer nonprovisional application (January 9, 1997), and even Burmer did not choose to use the primers of Carninci. Thus, the ordinarily skilled artisan would not have been motivated to combine the disclosures of Burmer and Carninci to make and use the claimed invention with any reasonable expectation of success. The Examiner therefore has not met the burden required to sustain a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully assert that a *prima facie* case of obviousness of the claimed invention cannot be established based on the disclosures of Burmer and Carninci. Reconsideration and withdrawal of the rejection of claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, and 32 under 35 U.S.C. § 103(a) are therefore respectfully requested.

IV. Other Matters

Applicants note that the Examiner has not considered Document Reference AS5, listed on the first page of the Form PTO-1449 filed together with the Third Supplemental Information Disclosure Statement on March 12, 2001. Applicants submit herewith another copy of Document Reference AS5, and request that the Examiner acknowledge consideration of the reference in the next Office Action.

V. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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